UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-FLW-LHG** **MDL No. 2738**
THIS DOCUMENT RELATES TO ALL CASES	

THE PLAINTIFFS' STEERING COMMITTEE'S MEMORANDUM IN RESPONSE AND OPPOSITION TO JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S MOTION TO EXCLUDE PLAINTIFFS' EXPERTS' OPINIONS REGARDING ALLEGED HEAVY METALS AND FRAGRANCES IN JOHNSON'S BABY POWDER AND SHOWER-TO-SHOWER

Table of Contents

TABLE OF AUTHORITIES

Cases

Other Authorities

The Plaintiffs' Steering Committee ("PSC") submits this Memorandum of Law in response and opposition to *Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Conditional Motion to Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals And Fragrances In Johnson's Baby Powder And Shower-to-Shower* [Dkt. No. 9736-4]. For the foregoing reasons, this Court should deny Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s (hereinafter "J&J") motion.

I. INTRODUCTION AND BACKGROUND

A. The J&J Talcum Powder Products are *mixtures* of numerous components, including heavy metals, fragrance chemicals, and fibrous talc

At the outset, it is important to understand that the J&J Talcum Powder Products at issue in this litigation—*Johnson's Baby Powder* and *Shower-to-Shower*[1]—are *mixtures* of numerous constituents, including platy talc, fibrous talc, asbestos, heavy metals, and fragrance chemicals.[2] Several of these constituents are established human carcinogens, including asbestos, fibrous talc, and the metals nickel and chromium (VI).[3] This opposition sets forth the PSC's opposition to J&J's

[1] Referred to herein as "Talcum Powder Products."

[2] *See* November 16, 2018 Report of Laura M. Plunkett, Ph.D., DABT ("Plunkett Report") at 18, attached hereto as **Exhibit 1**.

[3] IARC Monographs on Arsenic, Metals, Fibres, and Dusts: Volume 100 C, A Review of Human Carcinogens (2012), relevant excerpts attached hereto as **Exhibit**

challenges to the PSC's experts' opinions regarding three components of the Talcum Powder Products—heavy metals (chromium, nickel, and cobalt), the fragrances (which are themselves mixtures of numerous chemicals), and fibrous talc.

B. Heavy metals are present in the J&J Talcum Powder Products, including known human carcinogens chromium and nickel

The heavy metals nickel and chromium (VI) are human carcinogens.[4] Nickel, chromium (VI), chromium (III), and cobalt are all inflammatory agents.[5] The PSC's experts opine that these known carcinogens and/or inflammatory agents contribute to the inflammatory properties of the J&J Talcum Powder Products, thereby playing a role in the biologically plausible mechanism—inflammation—by which the Talcum Powder Products cause ovarian cancer. J&J largely ignores the PSC's experts' testimony about biological plausibility, instead arguing that it was necessary to consider dose response and thresholds of exposure to the individual metals in the products. For the reasons discussed in more detail below in **Section II A**, J&J's

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2 (Introduction and Preamble); Exhibit 3 (Nickel); and Exhibit 4 (Chromium); *See The Plaintiff Steering Committee's Opposition Defendants' Motion to Exclude Plaintiffs' Experts' Asbestos-Related Opinions*. J&J's fragrance is a mixture unto itself—the fragrance in Baby Powder is comprised of 141 constituents (some of which are themselves a mixture of chemicals) and the fragrance in Shower to Shower is comprised of 53 constituents.

[4] IARC, 2012 (**Exhibits 3 and 4**).

[5] IARC, 2012 (**Exhibits 3 and 4**); IARC Monograph on Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide: Volume 86 (2006), relevant excerpts attached hereto as **Exhibit 5**.

argument is without merit—neither Bradford Hill nor the EPA's guidance on qualitative analyses of mixtures requires dose assessments of the individual constituents in a mixed product. The PSC and its experts allege the Talcum Powder Products as *a whole* cause ovarian cancer, and the constituent parts play a contributing role.

It is beyond dispute that chromium, nickel, and cobalt are present in the J&J Talcum Powder Products. J&J's own internal documents and tests establish that the heavy metals are 1) present in the Vermont mines that were used to source the Talcum Powder Products for decades, and 2) present in the finished products as well.[6] J&J cannot plausibly dispute that the heavy metals are present, and instead argues that the PSC's experts' opinions about the metals are flawed because they

[6] *See* **Exhibit 6**, JNJ 000237076 (showing two Grade 66 samples from the Hammondsville mine in Vermont in 1991 contained high levels of chromium, cobalt and nickel); **Exhibit 7**, IMERYS 342524 (showing high levels of chromium, cobalt, and nickel in a 1997 annual composite sample of Grade 66 talc as measured using two different testing methods). Testimony from Imerys Talc America, Inc. employee Ms. Julie Pier establishes that testing was done on samples of finished products, *see* September 12-13, 2018 Deposition of Julie Pier ("Pier Dep."), attached hereto as **Exhibit 8** at 199:18-200:7 ("Q. A yearsly composit of the ore is made from each individual submission to be tested for metals. . .? . . .[I]ts on a yearly basis after the product is made."); Pier Dep. at 203:7-9 ("…there is post-finished-product testing as well by all of the methods, the XRD, PLM and TEM."); Pier Dep. at 413:5-7 ("Samples were taken…using…an automatic sampler while the silos are being filled of finished product."); Pier Dep. at 545:7-10 ("The quarterly finished product was from Vermont, and the finished product would have been Grade 66. Those were quarterly samples at that time."). For a more thorough recitation of test results, see the Rule 26 Expert Reports of Drs. Cook and Krekeler.

allegedly do not distinguish between the valence states of chromium—including chromium (VI) versus chromium (III)—and because they fail to consider the bioavailability of nickel. However, the PSC's experts acknowledge the valence states of chromium, but J&J's own testing did not distinguish between the two.[7] Regardless, the two most common forms of chromium contribute to the carcinogenicity of the products as a whole because they both cause inflammation. Likewise, J&J argues that the PSC's experts failed to consider the specific type and bioavailability of nickel in the products, but nickel (including all nickel compounds and metal) is classified by IARC as a Group 1 carcinogen in humans.[8] As explained below, the studies cited by J&J to support its argument only pertain to nickel *sulfates*, not the metal itself or its compounds. J&J's arguments regarding chromium and nickel fail for these and other reasons, discussed in detail in **Section II A**.

C. The secret chemicals in the J&J Talcum Powder Product fragrances are not in compliance with regulatory standards and contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products as whole

J&J *Baby Powder* is famous for its distinctive scent. However, the secret behind that fragrance is rather prosaic—a fragrance is nothing more than a mixture

[7] *See* **Exhibit 9**, JNJ 000237115-19 (J&J used the BPT 148 procedure to test samples of finished talcum powder products on an annual basis—as **Exhibit 9** makes clear, BPT 148 testing did not distinguish between the two forms of chromium).

[8] IARC, 2012 (**Exhibit 3**).

of chemicals. The FDA does not require companies to disclose the constituent chemicals in cosmetic fragrances to consumers, and J&J has therefore never revealed the identities of the chemicals in the *Baby Powder* and *Shower-to-Shower* fragrances to those who use the products. According to documents produced by J&J in this litigation, there are currently 141 chemicals in the *Baby Powder* fragrance and 53 chemicals in the *Shower-to-Shower* fragrance.[9]

To complicate things further, some of those chemicals are themselves mixtures of *other* chemicals.[10] J&J's documents also reveal that there have been changes to the fragrance formulas over the decades—for example, Benzene, ethenyl- (more commonly known as styrene) was a chemical used in the *Baby Powder* fragrance formula until J&J removed it in 2014.[11] As discussed in more detail below, styrene was long classified by IARC as a 2B carcinogen—meaning it was *possibly* carcinogenic to humans. Today, styrene is classified as a 2A carcinogen—it is a *probable* human carcinogen.[12] J&J did not provide information regarding the precise quantities of each chemical in the fragrances, nor has J&J clarified whether the

[9] *See* November 12, 2018 Expert Report of Michael M. Crowley, Ph.D. ("Crowley Report") at 12, attached hereto as **Exhibit 10**.

[10] *Id.* at 12.

[11] *Id.* at 20.

[12] *See* **Exhibit 11**, 2019 IARC 2A classification for styrene.

quantities of each chemical changed over the decades that the products have been sold to consumers.

The PSC's expert Dr. Michael Crowley offers two opinions about the J&J talcum powder product fragrance chemicals in this litigation: 1) they are not in compliance with government and industry standards (another way to put it—they raise regulatory concerns); and 2) the chemicals contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the J&J Talcum Powder Products as a whole.[13] Dr. Crowley conducted an exhaustive review of the available safety data and studies for each chemical and recorded the data in his report. He relies on his own education and extensive experience as a chemist who creates chemical formulations for use in consumer products to reach his opinions in this litigation. Despite his thorough review of the totality of evidence and his relevant experience in the field of chemical formulation, J&J argues that his opinions "lack good grounds," that they are unreliable because of a lack of studies linking the chemicals to *human ovarian* cancer specifically, and because he did not consider dose response. All of J&J's arguments are without merit for the reasons set forth in **Section II B** of this opposition.

[13] Crowley Report at 12.

D. Fibrous Talc, a known human carcinogen, is present in the J&J Talcum Powder Products

Talc (and other minerals) can occur in a *fibrous* form—this is referred to as being in the "asbestiform habit."[14] Fibrous talc and asbestos are not the same thing, but "fibrous talc occurring in an asbestiform habit has the same dangerous carcinogenic properties as asbestos."[15] Indeed, fibrous talc is classified as a known human carcinogen by IARC (a Group I carcinogen). The testing done by the PSC's experts Drs. Longo and Rigler in this litigation demonstrate that fibrous talc is present in the J&J Talcum Powder Products **98%** of the time.[16] The documents produced by J&J and Imerys Talc America, Inc. in this litigation also demonstrate that the mines used to source its Talcum Powder Products contained fibrous talc.[17] A table prepared by Dr. Krekeler labeled "Presence of Fibrous Talc in Defendants' Ore" lists several tests from both the Vermont and Italian mines that sourced J&J

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[14] *See* November 16, 2018 Expert Report of Mark Krekeler, Ph.D. ("Krekeler Report") at 3, attached hereto as **Exhibit 12**.

[15] *Id.* at 14, citing IARC, 2012.

[16] *See* January 15, 2019 Expert Report of William E. Longo and Mark W. Rigler ("Longo MDL Report") at 11, 15, attached hereto as **Exhibit 13** ("The MAS analysis showed fibrous talc in *41 of the 42* samples by the ISO PLM method and in three of the Blount PLM method.") (emphasis supplied).

[17] *See, e.g.*, **Exhibit 14**, JNJ 000085374; **Exhibit 15**, JNJ 000238826; **Exhibit 16**, JNJS71R_000009825; **Exhibit 17**, JNJ 000346572; **Exhibit 18**, JNJNL61_000027053; **Exhibit 19**, IMERYS 477879; and **Exhibit 20**, JNJS71R_000011316, all cited in Krekeler report at 23-29.

Talcum Powder Products where fibrous talc was detected—the tests spanned from 1945-1999.[18] To put it mildly, the "numerous examples showing [the] presence of fibrous talc are of significant concern both from a human health and from a quality control standpoint."[19]

There is overwhelming evidence that carcinogenic fibrous talc is present in J&J's Talcum Powder Products. In an attempt to exclude the PSC's experts' opinions about fibrous talc, J&J makes a strained argument that the PSC's experts have all somehow *misunderstood* the definition of fibrous talc. J&J further argues—without support—that its own documents *identifying and describing fibrous talc* are not actually referring to fibrous talc at all. J&J's arguments are without merit for the reasons set forth in **Section II C** of this opposition, and the PSC's experts' opinions about the carcinogenic fibrous talc that is present in J&J's Talcum Powder Products should not be excluded.

II. ARGUMENT

A. THE PSC'S EXPERTS' OPINIONS THAT THE HEAVY METALS PRESENT IN J&J TALCUM POWDER PRODUCTS PLAY A CONTRIBUTING ROLE IN CARCINOGENESIS ARE WELL-SUPPORTED AND RELIABLE

[18] Krekeler Report at 23-29.

[19] *Id.* at 14.

1. There is ample scientific evidence supporting the biologically plausible mechanism by which heavy metals operate to cause inflammation and carcinogenesis

J&J contends that "there is no scientific support for the theory that exposure to any of the heavy metals that the PSC's experts contend are present in talcum powder is capable of causing ovarian cancer."[20] This statement is incorrect with respect to all three of the heavy metals discussed by the PSC's experts: 1) both nickel and chromium VI have been classified by IARC as Group 1 carcinogens, meaning there is *sufficient evidence of carcinogenicity* in humans, and 2) cobalt has been classified by IARC as a Group 2B carcinogen, meaning it is *possibly carcinogenic* to humans.[21]

J&J's argument focuses exclusively on the lack of studies linking the heavy metals specifically to *ovarian* cancer in humans. When the IARC Working Group conducts a causation analysis, it considers the Bradford-Hill criteria.[22] IARC considers all available data relevant to a classification of carcinogenicity, including epidemiological and experimental studies and mechanistic and other relevant data.[23]

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[20] Def. Mem. at 1.

[21] IARC, 2006 (**Exhibit 5**).

[22] IARC, 2012 Preamble at 21 (**Exhibit 2**).

[23] IARC, 2012 Preamble at 12-14 (**Exhibit 2**). IARC defines 'carcinogenic' as "capable of increasing the incidence of malignant neoplasm, reducing their latency,

IARC also considers whether there is causation for multiple tumor types, temporality, effect, biological plausibility, changes at the cellular and molecular level, and the coherence of the overall data—the assessment *is not based on the availability of studies on a specific type of cancer*.[24]

The *sufficient evidence* of carcinogenicity standard needed for a Group 1 classification is met when, "a causal relationship has been established between exposure to the agent and human cancer."[25] Specific organs and tissues are identified where studies have specifically shown increased cancer risk, but the overall evaluation focuses on carcinogenicity where the agent acts through a 'relevant mechanism,' – findings applicable to all organs, including the ovaries.[26] This focus was discussed by Dr. Zelikoff, who refers to the extensive testing in cells and animals and states that there is no reason to believe the metals would not have the same carcinogenic effects in the ovary as they do in other organs.[27]

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or increasing their severity or multiplicity." *Id.* The terms 'neoplasm' and 'tumo[u]r' are used interchangeably. *Id.*

[24] IARC, 2012 Preamble at 21, 22 (**Exhibit 2**).

[25] *Id.* at 29.

[26] *Id.* at 30-32.

[27] *See* January 21, 2019 Deposition of Judith Zelikoff, Ph.D. ("Zelikoff Dep.") at 983:22-294:12, attached hereto as **Exhibit 21**.

IARC published a monograph evaluating the carcinogenic risks posed to humans by arsenic, metals, fibres, and dusts in 2012,[28] and published a monograph evaluating the carcinogenic risks posed to humans by cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide in 2006.[29] As part of the expert reviews, the IARC Working Group evaluated relevant data, including genetic effects, oxidative stress, DNA damage and repair, and cell proliferation. The Agency for Toxic Substances and Disease Registry (ATSDR) has also described the carcinogenic mode of action (or mechanism) for nickel: "The available evidence suggests that, mechanistically, nickel carcinogenicity is probably the result of genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) epigenetic factors. Additionally, certain nickel compounds promote cell proliferation, which would convert repairable DNA lesions into nonrepairable mutations. Nickel is considered to be genotoxic…"[30]

And according to the ATSDR, chromium (VI), chromium (V), and chromium (IV) "have all been shown to be involved in Fenton-like oxidative cycling,

[28] IARC, 2012.

[29] IARC, 2006.

[30] The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Nickel (August 2005) at 155, relevant excerpts attached hereto as **Exhibit 22**.

generating oxygen radical species…"[31] "It is believed that the formation of these radicals, which leads to oxidative stress, may be responsible for many of the deleterious effects of chromium on cells…"[32] ATSDR describes the mechanism of action for cobalt to include the following: "Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage…"[33] The NTP has listed chromium (VI)[34] and nickel[35] as "known to be human carcinogens", while cobalt is listed as "reasonably anticipated to be human carcinogens."[36]

IARC and the ATSDR both noted that the biological activities of all three metals, chromium (VI), cobalt, and nickel, result in inflammatory cell responses through oxidative stress, the formation of reactive oxygen species (ROS), and

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[31] The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Chromium (September 2012) at 281, relevant excerpts attached hereto as **Exhibit 23**.

[32] ATSDR, 2012 (**Exhibit 23**) at 282.

[33] The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Cobalt (April 2004) at 154, relevant excerpts attached hereto as **Exhibit 24**.

[34] National Toxicology Program (NTP), 14th Report on Carcinogens (2016), relevant excerpts regarding chromium, nickel, and cobalt attached hereto as **Exhibit 25**.

[35] *Id.*

[36] *Id.*

resultant DNA damage and genotoxic effects. These biologic activities are the same biologically plausible modes of action for Talcum Powder Products and ovarian cancer cited to by the PSC's experts. J&J's argument that there is insufficient evidence to support the PSC's experts' opinions about the heavy metals in *Baby Powder* and *Shower-to-Shower* and the biological mechanism by which they operate is without merit, and the opinions should not be excluded.[37]

2. A qualitative analysis is appropriate for assessing the safety of mixtures like J&J's *Baby Powder* and *Shower-to-Shower*

As stated above, J&J's *Baby Powder* and *Shower-to-Shower* are mixtures composed of numerous constituents, including platy talc, fibrous talc, asbestos, heavy metals (cobalt, nickel and chromium), and fragrance chemicals. Asbestos, fibrous talc, and the metals nickel and chromium are known human carcinogens. Mixtures are defined "as any combination of two or more chemical substances

[37] As *Daubert* specifically recognized, "cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof" are the ordinary means to attack an opposing expert. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 596 (U.S. 1993). The United States Supreme Court has recognized that there is a range in which experts might reasonably differ on issues of science, and that such conflicting evidence should be admitted to aid the jury in deciding those issues. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 1953 (1999); *Ambrosini v. Labarraque*, 101 F.3d 129, 138-139 (D.C. Cir. 1996); *Globetti v. Sandoz Pharm. Corp.*, 111 F.Supp. 2d 1174, 1176 (N.D. Ala. 2000).

regardless of source or of spatial or temporal proximity."[38] The EPA's Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures sets forth the human risk assessment process to use on mixtures like the J&J's Talcum Powder Products that contain carcinogenic components.[39]

The EPA specifically recognizes that "most frequently, *not all components of the mixture are known*, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited."[40] Where this occurs, as in the case with the J&J's Talcum Powder Products, the lack of quantitative data may lead the risk assessor to decide that *a qualitative analysis should be performed*.[41] This generally occurs in cases where data quality is poor, adequate quantitative data is not available, data on a similar mixture cannot be classified as sufficiently similar to the mixture of concern, exposures cannot be characterized with confidence, or where method-specific assumptions about the toxicologic action of the mixture or its components cannot be met.

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[38] USEPA 2000 "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures," 2000 at Appendix A, A-1. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533 (last accessed May 23, 2019), relevant excerpts attached hereto as **Exhibit 26**.

[39] *Id.*

[40] *Id.* at Appendix A, A-1 (emphasis supplied).

[41] *Id.* at 11.

A qualitative assessment is appropriate for characterizing the potential human health impacts from exposure to mixtures in these situations.[42] In the case of mixtures containing known carcinogens, the default approach is to assume that there are additive effects among the constituents, or "potential interactions among the components."[43] This approach is appropriate for assessing the J&J's Talcum Powder Products—which again, are mixtures containing known carcinogens—and is fully supported by the PSC's experts and the scientific literature.

3. Proof of causation, dose response, and thresholds of exposure are not required as part of a qualitative risk assessment and are not necessary to support the PSC's experts' opinions because there are established "biologically plausible" mechanisms explaining how the heavy metals promote cancer

J&J incorrectly asserts that proof of causation, dose-response, and thresholds of exposure are *required* to support the PSC's experts' opinions about the heavy metals in the products. However, these factors are not required under the qualitative risk assessment process approved by the EPA and described above. Nor does the Bradford-Hill analysis require a dose assessment of the individual constituents in mixed products like the J&J's Talcum Powder Products. Rather, the Bradford-Hill dose response analysis looks at the duration and frequency of exposure of the entire

[42] *Id.*

[43] *Id.* at A-7.

product with reference to the epidemiological data as a whole.[44] The PSC's allegation is that the J&J's Talcum Powder Products as a whole—that is, *the mixture of all constituent parts*—cause ovarian cancer, not any single constituent part acting alone.

And, dose-response and threshold determinations are distinct and separate from the Bradford Hill *biologic plausibility mode of action* that the PSC's experts' opinions are based on. The term "mode of action" is defined by the USEPA as "a series of key events and processes starting with interaction of an agent with a cell and proceeding through operational and anatomical changes causing disease formation."[45] This definition is also consistent with the Bradford-Hill aspect of plausibility.

Biologic plausibility (one of the Bradford-Hill aspects of association) "depends upon existing knowledge about the mechanisms [mode of action] by which the disease develops [and] on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works." [46] "What is

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[44] *See* the PSC's *Memorandum of Law in Response and Opposition to Defendants' Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Motion to Exclude Plaintiffs' General Causation Opinions* ("*PSC Gen. Causation Opp.*").

[45] USEPA, 2000 (**Exhibit 26**) at 10.

[46] Reference Manual on Scientific Evidence, Reference Guide on Epidemiology, Third Edition (2011) at 604-05.

biologically plausible depends upon the biological knowledge of the day."[47] Given the complexity of cancer biology, a biologically plausible mechanism should not have to establish "all levels of scientific explanation" for "each step" in the cancer process as this is "too stringent" and "overdemanding."[48] What is required, however, is that the proposed "mode of action and the events that are part of it be based on current understanding of the biology of cancer to be accepted."[49] The use of an adverse pathway model is also a recognized approach to determining a biological plausible mechanism. In this model, the chemical toxicities and properties of a chemical [toxicant] is first considered and characterized then followed along a toxicity pathway that investigates the toxicants molecular (DNA) interaction and impact, cellular responses, and organ responses followed by an investigation of population responses (epidemiology).[50]

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[47] Hill, A.B., The Environment and Disease. *Proc R Soc Med*; 1965, 58(5):295-300, attached hereto as **Exhibit 27**.

[48] Weed, D.L. and Hursting, S.D. Biologic Plausibility in Causal Inference: Current Method and Practice. *Am J Epidemiology;* 1998, 147(5): 415-425, 421, attached hereto as **Exhibit 28**.

[49] Golden, R., Pyatt, D., Shields, P.G. Formaldehyde as a Potential Human Leukemogen: An Assessment of Biological Plausibility. *Crit Rev Toxicology;* 2006, 36(2):135-153, 148, attached hereto as **Exhibit 29**.

[50] Dailey, J., Rosman, L., Silbergeld, E.K. Evaluating Biological Plausibility in Supporting Evidence for Action through Systematic Reviews in Public Health. *Public Health.* 2018; 165:48-57, attached hereto as **Exhibit 30**.

This is precisely the model the PSC's experts appropriately used to assess the role of the constituent parts of the J&J Talcum Powder Products, and their respective testimony is consistent regarding the heavy metals' biologically plausible mechanism—inflammation:[51]

- **Dr. Carson** testified that a dose response assessment is not necessary as part of a qualitative analysis: "A qualitative risk assessment does not necessarily require a dose-response in order to reach valid conclusions."[52]

- **Dr. Carson** also testified that the heavy metals contribute to the inflammatory process and carcinogenicity: "…my opinion is that any [amount of nickel, chromium, cobalt] within the microenvironment of the inflammatory process that is occurring due to talc sequestration is contributing to the carcinogenic potential."[53]

- **Dr. Levy** testified that chronic inflammation is a well-established biologic mechanism of cancer, including ovarian cancer, both in the initiation and the progression of the cancer.[54] He described the role of inflammation in cancer as a "fundamentally accepted aspect of cancer biology"[55] and not a "hypothetical."[56] Dr. Levy further

[51] Constituents of Talcum Powder Products with a contributory role in ovarian cancer risk include platy talc, heavy metals (chromium, nickel and cobalt), asbestos and fibrous talc.

[52] *See* January 19, 2019 Deposition of Arch I. "Chip" Carson, M.D., Ph.D. ("Carson Dep.") at 173:8-10, attached hereto as **Exhibit 31**.

[53] *Id.* at 171:16-21.

[54] *See* January 11, 2019 Deposition of Shawn Levy, Ph.D. ("Levy Dep.") at 116:17-24 and 117:1-2, attached hereto as **Exhibit 32**.

[55] *Id.* at 263:2-17.

[56] *Id.* at 294:1-14.

described the established carcinogenic mechanisms of chromium and nickel to include "DNA damage, mutation, genomic instability, and cell transformations."[57] He stated that cobalt was "shown to increase production of reactive oxygen species (ROS) and other inflammatory and proliferative changes."[58] The presence of the known carcinogens nickel and chromium, as well cobalt, which is "reasonably anticipated" to be carcinogenic, in talcum product supports his opinion that the Talcum Powder Products cause inflammation.[59]

- **Dr. Zelikoff** testified, "There is no literature that says you need one particle or ten particles. The inflammatory response that nickel causes is extremely well established, even at very low concentrations. And…the same is true for hexavalent chromium and for chromium, trivalent chromium."[60] She further explained that "a single exposure to a certain concentration, whatever that concentration is, can produce effects…it can start the process of either inflammation or oxidative stress."[61]

- **Dr. Plunkett** testified that, "Inflammation is a well-studied mechanism of carcinogenesis."[62] In outlining the role of inflammation in cancer, Dr. Plunkett explained: "there are several basic facts about inflammation and cancer that include the following: (1) chronic inflammation increases cancer risk; (2) subclinical, often undetectable inflammation may be as important in increasing cancer risk; (3) various types of immune and inflammatory cells are frequently present within tumors;

[57] *See* November 16, 2018 Expert Report of Shawn Levy, Ph.D., ("Levy Report") at 16, attached hereto as **Exhibit 33**.

[58] *Id.* at 16.

[59] *Id.*at 16.

[60] Zelikoff Dep. at 293:1-11 and 282:1-24.

[61] *Id.* at 368:10-369:15.

[62] Plunkett Report at 45.

(4) immune cells affect malignant cells through production of cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species; (5) inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression; (6) in developing tumors anti-tumorigenic and pro-tumorigenic immune and inflammatory mechanisms coexist, but if the tumor is not rejected, the pro-tumorigenic effect dominates; (7) signaling pathways that mediate the pro-tumorigenic effects of inflammation are often subject to a feed-forward loop; and (8) certain immune and inflammatory components may be dispensable during one stage of tumorigenesis but absolutely critical in another stage."[63]

- For the Talcum Powder Products and their heavy metal constituents (cobalt, chromium, and nickel), **Dr. Plunkett** concluded, "…the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to carcinogenesis and that the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to Talcum Powder Products likely involves induction of a chronic inflammatory response. A review of the IARC monographs for talcum powder product constituents, such as asbestiform talc and non-asbestiform talc, nickel, cobalt, and chromium, reveals similarities in the biological effects that are discussed as underlying the carcinogenic potential of the individual compounds."[64]

- **Dr. Plunkett** further explained that, " the available data relating to mechanism of carcinogenicity of Talcum Powder Products, where the body powders are a mixture of compounds with carcinogenic hazard, indicate that the

[63] *Id.* at 45.

[64] *Id.* at 46.

various compounds in Talcum Powder Products would be expected to produce at least an additive effect on the risk of cancer based on their ability to induce similar biological responses that underly[sic] carcinogenesis."[65] Dr. Plunkett also explained that the three heavy metals (cobalt, chromium, and nickel) have a similar biological plausibility mechanism—they cause irritation and inflammation.[66]

- **Dr. Plunkett** also discussed the complex mixture of J&J Talcum Powder Products, indicating that "when you have a complex mixture that has added to it things like asbestos and heavy metals, because I talk about the additivity issue that can come to play. So that -- in other words, [there is an] increased risk when you have a complex mixture with additional components that all share the same toxic properties as far as target organs or types of effects or mechanisms that are triggered in the body."[67]

- **Dr. Carson** similarly recognized that "talcum powder may contain varying amounts of chromium, cobalt and nickel, metal ions that are recognized as cancer causing."[68] Dr. Carson reported, "these ions leach out of the talcum powder slowly over time, resulting in continuous, low-level exposure of the surrounding tissues to carcinogenic metals"[69] and that "the presence of carcinogenic metals such as, chromium, cobalt and nickel, and toxic fragrance components in commercial Talcum Powder Products,

[65] *Id.* at 47.

[66] *See* December 19, 2018 Deposition of Laura Plunkett ("Plunkett Dep.") at 268:7-13, attached hereto as **Exhibit 34**.

[67] *Id.* at 146:11-21.

[68] *See* November 16, 2018 Expert Report of Arch "Chip" Carson, M.D., Ph.D. ("Carson Report") at 5, attached hereto as **Exhibit 35**.

[69] *Id.* at 5.

> adds to their carcinogenic potency."[70] In describing the mode of action of these metals, Dr. Carson reported that they are "liberated in bodily fluids and tissues and are free to exert their carcinogenic effects"[71] and "once reaching the target tissues, talcum powder and its constituents initiate carcinogenesis via multiple means, including, inflammation with chemotaxis of inflammatory cells, liberation of cytokines, and reactive oxygen species, inactivation of TP53 genetic modulator, inhibition of DNA repair, and long-term promotion of genetic mutations via continuous inflammation and cellular growth stimulation."[72]

As discussed in great detail above, the PSC's experts did not need to conduct a dose response assessment of the individual constituents because they evaluated the Talcum Powder Products as a whole—that is, *as a mixture* of the constituents. It is the *entire* product, including its constituents, that trigger carcinogenesis.[73] Further, as Dr. Zelikoff testified, it would be difficult if not impossible to analyze the talc separately from all of the other constituent parts in the products: "I'm not even sure how that would be done or I don't think it could be done."[74] Dr. Zelikoff further explained that there are *in vitro* studies where the products containing the constituent parts were applied to human ovarian cells and caused an inflammatory response:

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[70] *Id.* at 7.

[71] *Id.* at 8.

[72] *Id.* at 10.

[73] Zelikoff Dep. at 270:20-271:16.

[74] Zelikoff Dep. at 271:18-272:4.

"…in vitro studies like those of [Dr.] Saed who looked for oxidative stress…[and Dr.] Shukla…who also looked at…human ovarian cells…[and] changes in gene expression associated with oxidant production and reactive oxygen species production."[75]

4. J&J has no factual basis for its argument that Chromium (VI), an inflammatory agent and known carcinogen, is not present in the Talcum Powder Products

J&J argues that the PSC's experts' opinions are unreliable because they "ignore" the valence state of chromium found in talc. J&J's experts assert "if chromium is present in talc products, it is most likely in the form of chromium (III)".[76] J&J makes unsubstantiated guesses about what is "most likely" in the J&J Talcum Powder Products in an attempt to minimize the PSC's experts' opinions

[75] Zelikoff Dep. at 296:16-297:14; *see* Fletcher, NM, Harper AK, Memmaj I, Fan R, Morris, RT, Saed, GM. "Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer." Reprod. Sci. 2019 Feb 28:1933719119831773. Doi: 10.1177/1933719119831773, attached hereto as **Exhibit 36**. Saed, Ghassan M., Robert T. Morris, and Nicole M. Fletcher. *Chapter 4: New Insights of into the Pathogenesis of Ovarian Cancer: Oxidative Stress.* (October 24, 2018), attached hereto as **Exhibit 37**. Shukla, Arti, Maximilian B. MacPherson, Jedd Hillegass, Maria E. Ramos-Nino, Vlada Alexeeva, Pamela M. Vacek, Jeffrey P. Bond, Harvey I. Pass, Chad Steele, and Brooke T. Mossman. 2009. "Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity." *American Journal of Respiratory Cell and Molecular Biology* 41 (1): 114–23. https://doi.org/10.1165/rcmb.2008-0146OC.), attached hereto as **Exhibit 38**.

[76] Def. Mem. at 34.

regarding the presence of a *known carcinogen*—chromium (VI). The PSC's experts agree with J&J's experts that chromium exists in different forms, and that the most prevalent forms are chromium (III), or trivalent chromium, and chromium (VI), or hexavalent chromium. Experts for the PSC and J&J also agree that chromium (VI) is a carcinogen[77] and is "strongly oxidizing,"[78] which the NTP and Dr. Zelikoff explain essentially means irritating, corrosive, and toxic systemically.[79] The PSC's general causation case is based in part on the fact that Talcum Powder Products cause inflammation at the site of the ovary and/or fallopian tube and inflammation causes ovarian cancer. Chromium (VI) is an inflammatory agent as, to an extent, is chromium (III),[80] both of which contribute to the inflammatory milieu that results in the development of epithelial ovarian cancer.

First, J&J acknowledges that chromium (VI) is a carcinogen, but claims that "few of those studies provide 'adequate exposure data for use in risk estimation.'"[81]

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[77] *See* February 25, 2019 Expert Report of Kelly Scribner Tuttle, Ph.D., CIH ("Tuttle Report") at 37-38, attached hereto as **Exhibit 39**; *see also* April 4, 2019 Deposition of H. Nadia Moore, Ph.D., DABT, ERT ("Moore Dep.") at 287:7-8, attached hereto as **Exhibit 40**; see also February 25, 2019 Expert Report of H. Nadia Moore, Ph.D., DABT, ERT ("Moore Report") at 53, attached hereto as **Exhibit 41**.

[78] Moore Report at 52; *see also* November 16, 2018 Expert Report of Judith Zelikoff, Ph.D. ("Zelikoff Report") at 10, attached hereto as **Exhibit 42**.

[79] NTP, 2016 (**Exhibit 25**); *see also* Zelikoff Report at 10.

[80] IARC Monograph on Chromium, Nickel and Welding, Volume 49 (1990), relevant excerpts attached hereto as **Exhibit 43**; IARC, 2012 (**Exhibit 4**).

[81] Def. Mem. at 32.

J&J makes this assertion even though its experts and the PSC's experts cite to agencies like IARC to verify chromium (VI)'s status as a human carcinogen. IARC considered dose as part of its determination that chromium is a Group I carcinogen—specifically, it used a Bradford Hill analysis as the framework for determining causation.[82] Under those rigorous standards, IARC considered dose ranges, dose that reached the target (exposure) and dose-response data.[83] The NTP also concluded that chromium (VI) compounds are carcinogenic in humans in its 14th Report on Carcinogens.[84] In doing so, the NTP specifically evaluated human exposure, as well as toxicokinetics, mechanism, and studies in humans and animals.[85] The PSC's experts evaluated the Talcum Powder Products as a whole because it is the entire product (the mixture of all constituents), that trigger carcinogenesis.[86] Indeed, the

[82] IARC, 2012 (**Exhibit 2**).

[83] *Id.* at 24, 25, 28, 31.

[84] NTP, 2016 (**Exhibit 25**).

[85] *Id.* at 2.

[86] *See* Carson Report at 8; *see also* Plunkett Report at 47 ("[w]hen considered together with general principles of toxicology, the available data relating to mechanism of carcinogenicity of talcum powder products, where the body powders are a mixture of compounds with carcinogenic hazard, indicate that the various compounds in talcum powder products would be expected to produce at least an additive effect on the risk of cancer…"); *see also* February 7, 2018 Deposition of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Dep.") at 137:9-12, attached hereto as **Exhibit 44** ("To the degree that [heavy metals, asbestos and fibrous talc] are all part and parcel of the same product, they're not – I wouldn't think of them as contaminants"); Zelikoff Dep. at 270:20-271:16.

presence of constituents like heavy metals were evaluated as part of the total risk profile.[87] And, *in vitro* studies where talcum powder product is applied demonstrate a cellular response,[88] demonstrating a reaction to the product as a whole, including constituents like heavy metals. Further, the PSC's experts clarify that "a single exposure to a certain concentration, whatever that concentration is, can produce effects…it can start the process of either inflammation or oxidative stress."[89]

Second, J&J's expert Dr. Moore states in her report that chromium (VI) "has been shown to be a carcinogen with high occupational exposures of airborne chromium (VI) associated with increased risk of respiratory (lung) cancer (but not dermal)."[90] This statement is misleading because it insinuates that an assessment has not been done for dermal routes such as the perineum. The IARC Working Group considers all available data relevant to an assessment of carcinogenicity, including epidemiological and experimental studies and mechanistic and other relevant data,[91]

[87] Carson Report at 6, 7; Plunkett Dep. at 226:8-10 ("What people are exposed to is the complex mixture, not just each one of those individual components.").

[88] Zelikoff Dep. at 296: 16-297:14; *see also* **Exhibits 36, 37, and 38**.

[89] Zelikoff Dep. at 368:10-369:15; *see also* Carson Dep. at 171:16-21.

[90] Moore Report at 1.

[91] IARC, 2012 (**Exhibit 2**). IARC defines 'carcinogenic' as "capable of increasing the incidence of malignant neoplasm, reducing their latency, or increasing their severity or multiplicity." (*Id*. at 12). The terms 'neoplasm' and 'tumo[u]r' are used interchangeably. (*Id.*).

and the NTP has a similar process.[92] Consideration is given to whether there is causation for multiple tumor types, the temporality, effect, biological plausibility, changes at the cellular and molecular level and coherence of overall data; it is not based on availability of studies on a specific cancer type.[93] When sufficient evidence is found to classify it as a Group I carcinogen, "a causal relationship has been established between exposure to the agent and human cancer." Specific organs and tissues are identified where studies have specifically shown increased cancer risk,[94] but the overall evaluation is of carcinogenicity where the agent acts through a 'relevant mechanism,' – findings applicable to all organs, including the ovaries.[95] This is supported by both Drs. Plunkett and Zelikoff who point out the similarity in the mechanism of carcinogenesis established by both *in vitro* and *in vivo* studies.[96]

Third, J&J asserts that the PSC's experts attribute chromium in talcum powder to contributing to the product's carcinogenic effects without distinguishing between valence states. This contention is simply untrue, as the difference between the

[92] NTP, 2016 (**Exhibit 25**).

[93] IARC, 2012 (**Exhibit 2**).

[94] Available studies that involved chromium carcinogenicity in humans consisted of lung and nose and nasal sinuses, as cited by IARC, 2012.

[95] IARC, 2012 (**Exhibit 2**).

[96] *See* Plunkett Dep. at 273:7-274:1 ("…regardless of where the cancer is developing, the fact that these compounds have the ability to stimulate similar toxic responses in tissues could lead to…cancer development."); *see also* Zelikoff Dep. at 293:22-294:12.

valence states is pointed out in numerous PSC's experts' reports.[97] Further, Dr. Cook testified that he is aware of the distinction between chromium III and IV, as they are the two forms most often associated with rock, and explained that the testing procedures done by J&J "would not distinguish between the two."[98] Dr. Krekeler also testified that he saw no regular testing performed by J&J or Imerys Talc America, Inc. that distinguished the between amount of hexavalent versus trivalent chromium in the finished products.[99]

Cellular response to chromium depends on the form of the chromium.[100] The form of the chromium in turn depends upon its environment, as Dr. Carson explained at his deposition: the specific valence state of chromium in cosmetic talc is "dependent on the surrounding structure that the metals are contained in, and the metals can assume a different valence state depending on the redox environment."[101]

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[97] Zelikoff Report at 9; Krekeler Report at 7; *see also* November 15, 2018 Expert Report of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Report") at 16, attached hereto as **Exhibit 45**.

[98] *See* January 30, 2019 Deposition of Robert Cook, Ph.D. ("Cook Dep.") at 402:15-404:10, attached hereto as **Exhibit 46**.

[99] *See* January 25, 2019 Deposition of Mark Krekeler, Ph.D. ("Krekeler Dep.") at 313:1-314:15, attached hereto as **Exhibit 47**; *see* **Exhibit 9**, JNJ 000237115-19 (J&J used the BPT 148 procedure to test samples of finished talcum powder products on an annual basis—as **Exhibit 9** makes clear, BPT 148 testing did not distinguish between the two forms of chromium).

[100] Zelikoff Dep. at 321:2-321:20.

[101] Carson Dep. at 180:17-181:3.

Dr. Plunkett explained that both chromium (III) and chromium (VI) have toxic properties, with varying levels of safe exposure.[102] And Dr. Smith-Bindman specifically distinguishes the chromium (VI) valence state when she describes its mechanism of carcinogenicity in her report.[103] Clearly, the PSC's experts are aware of the potential valence states of chromium.[104] However, their opinions are necessarily based on J&J's historical testing data from 1972 through 2003 that J&J made available in this litigation. J&J was aware of the different valence states of chromium but selected a testing procedure that failed to distinguish between chromium (III) and chromium (VI).[105] Having failed to conduct the necessary testing, J&J cannot now ask the court to assume that all chromium found was chromium (III).

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[102] Plunkett Dep. at 411:11-16 ("Both chrome III and chrome VI have toxic properties, specifically irritant properties as well, but they may be looked at separately, for example, in the regulatory context when you set safe levels of exposure.")

[103] Smith-Bindman Report at 16.

[104] All of the PSC's experts who refer to the carcinogenicity of chromium cite to IARC, 2012, which clearly and specifically discusses the carcinogenicity of chromium (VI) as distinguished from chromium (III).

[105] Cook Dep. at 403:21-404:4 ("…the technique used by Johnson & Johnson would not distinguish between the two, and their – their specs don't try to distinguish between the two"); *see also* Plunkett Dep. at 411:2-7 ("Ionic chromium as detected within the documents that – where the measurement were made of the actual talc samples that were processed and made into baby powder, which did not necessarily distinguish between chrome III and chrome VI.").

Fourth, J&J criticize the PSC's experts for not offering an opinion as to which valence state of chromium is present in the Talcum Powder Products. Again, this is an unfair criticism because none of the routine testing that J&J or Imerys Talc America, Inc. performed on talc ore or Talcum Powder Products differentiated between the chromium (III) and chromium (VI) valence states. Further, the PSC's experts did not engage in their own testing of talc ore or powder samples for heavy metals. Rather, they reviewed and reported on J&J's and Imerys Talc America, Inc.'s testing and the testing performed by third parties on their behalves. J&J focuses its criticism on Drs. Cook and Krekeler, both of whom not only acknowledge that chromium has different valence states, but also highlight J&J's use of a deficient testing methodology that cannot distinguish between a chromium (III) to chromium (VI) ratio.[106] Additionally, J&J knew that chromium (VI) exists in talc mines—that knowledge is reflected in internal documents reviewed by the PSC's experts.[107] Plaintiffs know of only one instance where J&J tested for chromium (VI) in "Talc

[106] Cook Dep. at 403:21-404:10 ("…the technique used by Johnson & Johnson would not distinguish between [[chromium (III) versus chromium (VI)], and their – their specs don't try to distinguish between the two…"); *see also* Krekeler Report at 36 ("No routine testing was done to determine the ratio of Chromium III to Chromium VI.").

[107] **Exhibit 48**, JNJ 000131754 at 755 ("In mine the Chromium exists mainly as Hexavalent chromium and Chromium trioxide. Hexavalent chromium is the most toxic compound among all of chromium oxide…").

Powder" samples, and in that analysis, chromium (VI) was present at an average of 75 ppb.[108]

Fifth, and finally, J&J argues that the PSC's experts do not have evidence to suggest that "chromium (VI) is more likely to be found" in the Talcum Powder Products than chromium (III). Chromium (VI) is most commonly derived from industrial processes but is also produced naturally through the oxidation of chromium (III) by manganese minerals,[109] and chromium (VI) is soluble in water.[110] Chromium is found at concentrated levels in the ultramafic rock of the Earth's crust,[111] the very rock found in Vermont that is altered into serpentinites and talc. Heavy metals are frequently contained in chlorite species, which are consistently reported as abundantly present in core logs[112] from the Argonaut mine,[113] as well as in other internal reports and studies.[114] High levels of heavy metals including

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[108] **Exhibit 49**, JNJ 000378046, document was reviewed by Plaintiffs' expert Dr. Cook.

[109] Oze, C., Bird, D.K., Fendorf, S. Genesis of hexavalent chromium from natural sources in soil and groundwater. PNAS. April 2007; 104(16):6544-6549, attached hereto as **Exhibit 50**.

[110] IARC, 2012 (**Exhibit 4**).

[111] Oze, 2007.

[112] 'Core logs' refers to the recorded lithology (rock types) and mineralogy of sections of cylindrical core drilled from rock or a mineral deposit.

[113] *See, e.g.*, **Exhibit 51**, IMERYS 469483 at 484.

[114] **Exhibit 52**, IMERYS 441340 at 364 (average chlorite content is 4.01% according to a 2008 ore reserve study).

chromium, cobalt, and nickel were consistently found in the talc ore from Vermont talc mines used to source J&J talc between 1972 and 2003.[115] More importantly, high levels of the same heavy metals were likewise found *in the finished Grade 66 product* from the Vermont mines used in the J&J Talcum Powder Products.[116] The PSC's experts Drs. Cook and Krekeler document the existence of heavy metals in the finished products in their reports.[117]

The chromium levels measured well over *200 ppm* in many samples of both the talc ore and talcum powder product when J&J's specification limit for chromium in Talcum Powder Products was only *0.5 ppm*.[118] Additionally, J&J's and Imerys Talc America, Inc's internal documents indicate they were aware chromium (VI) was present both in the talc mines[119] *and in the finished products*—this explains

[115] **Exhibit 53**, JNJ 000246437 (shows high levels of chromium, cobalt, and nickel in a 1990 sample from the Hamm mine in Vermont).

[116] **Exhibit 6**, JNJ 000237076 (showing two Grade 66 samples from the Hammondsville mine in Vermont in 1991 contained high levels of chromium, cobalt and nickel); **Exhibit 7**, IMERYS 342524 (showing high levels of chromium, cobalt, and nickel in a 1997 annual composite sample of Grade 66 talc as measured using two different testing methods); *see also* Ex. C to Zelikoff Report which includes additional test results showing high levels of heavy metals in Grade 66 talc from Vermont.

[117] *See* November 16, 2018 Expert Report of Robert Cook, Ph.D. ("Cook Report") at 28-34, attached hereto as **Exhibit 54**; Krekeler Report at 31-33.

[118] *See* June 28-29, 2018 Deposition of Donald Hicks ("Hicks Dep.") at 79:1-3, attached hereto as **Exhibit 55**.

[119] **Exhibit 48**, JNJ 000131754.

J&J's single test to determine the ratio of chromium valence states.[120] And contrary to J&J's assertions, the 1968 study cited by Dr. Zelikoff supports the presence of chromium (VI) in Vermont talc mines. J&J has historically held a market share majority for cosmetic Talcum Powder Products,[121] and it began sourcing talc for its products from Vermont no later than 1966.[122] Accordingly, the samples tested in the 1968 study—which included twenty-two off-the-shelf products consisting of body powder, bath powder and all-purpose powder—would have contained talc derived from Vermont mines.[123]

5. J&J has no factual basis for its argument that the form of nickel present in the J&J Talcum Powder Products is not carcinogenic

J&J seeks to exclude the PSC's experts' opinions on the carcinogenicity of nickel on the basis that the specific form of nickel determines its bioavailability and thus its carcinogenicity. However, J&J fails to cite any support for why the specific

[120] **Exhibit 49**, JNJ 000378046.

[121] **Exhibit 56**, JNJ 000300223, Johnson & Johnson performed a market share data study in 1976 to determine major volume brands. At this point in time J&J Baby Powder accounted for 53.6% of the body powder market while J&J Shower-to-Shower accounted for 11.1% of the market bringing J&J's total body powder market share to 64.7%.

[122] *See* February 25, 2019 Expert Report of Mary Poulton, Ph.D. ("Poulton Report") at 3, attached hereto as **Exhibit 57**.

[123] Cralley, L. J., Key, M. M., Groth, D.H., Lainhart, W. S., and Ligo, R. M. 1968. Fibrous and mineral content of cosmetic talcum products. *American Industrial Hygiene Association Journal.* 29(4):350-354, attached hereto as **Exhibit 58**.

form of nickel found in the Talcum Powder Products would lack carcinogenicity, particularly when nickel (including all nickel compounds and metal) is classified by IARC as a Group 1 carcinogen in humans.[124]

To support its argument, J&J cites two animal studies where nickel compounds did not induce tumors.[125] However, J&J apparently fails to recognize that the carcinogenic effects of nickel differ between animals and humans and only *certain* nickel compounds are considered Group I carcinogens in animals.[126] This could, in part, be due to differences in systemic processing, as it does not tend to bioaccumulate in animals.[127] While it is true that the two animal studies cited by J&J did not indicate any effects of nickel compounds in rats, this is to be expected, because the compound applied in both was *nickel sulfate hexahydrate*—nickel sulfates have only "limited evidence" of carcinogenicity in animals.[128] As J&J argues, "it is important to know the specific form of nickel." That is certainly the case here, yet J&J's argument rests solely on studies pertaining to a nickel sulfate rather than *all* nickel compounds and nickel metal, which are Group I carcinogens.[129]

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[124] IARC, 2012 (**Exhibit 3**).

[125] Def. Mem. at 37.

[126] IARC, 2012 (**Exhibit 3**) at 210.

[127] ATSDR, 2005 (**Exhibit 22**) at 12.

[128] IARC, 2012 (**Exhibit 3**) at 211.

[129] *Id.* at 210.

J&J further argues that the PSC's experts do not take the bioavailability of nickel into account in rendering their opinions.[130] This is inaccurate. In evaluating the health effects of nickel, the PSC's experts considered, in part, the analyses of agencies such as IARC and the NTP.[131] These agencies base their carcinogenicity analyses on many types of relevant data. For example, IARC considers the Bradford Hill criteria for causality.[132] IARC considers all available data that is relevant to the question of carcinogenicity, including epidemiological and experimental studies and mechanistic and other relevant data, including the chemical form of the material in question.[133] In addition to simply considering nickel's carcinogenicity, nickel's mechanism of action must be considered. Studies indicate that the immune system is one of the primary targets of nickel toxicity.[134] This is especially relevant because the Plaintiffs' general causation case is based in part on the fact that Talcum Powder Products cause inflammation and inflammation causes cancer. J&J's argument that nickel's contribution to carcinogenicity lacks a scientific basis is contrary to the evidence and lacks a valid foundation.

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[130] Def. Mem.at 37.

[131] Nickel compounds are known human carcinogens (NTP, 2016).

[132] IARC, 2012 Preamble (**Exhibit 2**) at 21.

[133] *Id.* at 13-14.

[134] ATSDR, 2005 (**Exhibit 22**) at 12.

In sum, chromium, nickel, and cobalt are present in the Vermont talc mines used to source J&J Talcum Powder Products and in the finished Talcum Powder Products themselves. Chromium (VI) and nickel are known human carcinogens. Chromium (VI), chromium (III), nickel, and cobalt are all known inflammatory agents. As carcinogens and/or inflammatory agents, the heavy metals all contribute to the inflammatory properties of the J&J Talcum Powder Products as whole, and thereby play a role in the biologically plausible mechanism—inflammation—by which the Talcum Powder Products cause ovarian cancer. None of J&J's arguments herein demonstrate otherwise, and J&J's attempt to exclude the PSC's experts' opinions about the heavy metals should be denied.

B. DR. MICHAEL CROWLEY'S OPINIONS REGARDING THE FRAGRANCE CHEMICALS IN THE J&J TALCUM POWDER PRODUCTS ARE WELL-SUPPORTED AND RELIABLE

1. J&J mischaracterizes Dr. Crowley's experience and the opinions he offers in this litigation

J&J's attempts to exclude Dr. Michael Crowley's opinions as an expert rest on mischaracterizations of his experience, methodology, and the very nature of the opinions he offers in this litigation. Dr. Crowley is not offering a causation opinion—that is, he was not asked to opine as to whether or not the chemicals that make up the fragrances used in J&J Talcum Powder Products *can or do cause* ovarian cancer. Rather, he was asked to review the available data that is accepted

and used by those in the "chemical formulation" business—like himself—to answer two questions about the fragrance chemicals used in J&J Talcum Powder Products. Put simply, Dr. Crowley wears his "chemist" or "chemical formulator" hat to address the following issues: 1) whether the fragrance chemicals are in compliance with government and industry standards; and 2) whether the fragrance chemicals can contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the J&J Talcum Powder Products as a whole.

Dr. Crowley is, first and foremost, a chemist. He earned his B.S. in chemistry from the University of Missouri-St. Louis, his M.A. in organic chemistry from Washington University in St. Louis, and his Ph.D. in molecular pharmaceutics from the University of Texas.[135] He has served as a consultant to more than 50 companies, primarily in the pharmaceutical industry, in the areas of proof of concept, formulation and product development, drug delivery and clinical development, including generation of FDA regulatory submissions.[136] Previously, he worked for a startup pharmaceutical company that developed novel drug products to treat infectious disease, as well as a contract research organization that provided formulation and drug product development services.[137] He is offered as an expert in

[135] Crowley Report at 14; *see also* January 4, 2019 Deposition of Michael Crowley, Ph. D. ("Crowley Dep.") at 341:20-23, attached hereto as **Exhibit 59**.

[136] Crowley Report at 14.

[137] *Id.* at 14.

chemistry and chemical formulation and has ample experience studying, reviewing, and assessing the safety of all types of chemicals, including several that are in the J&J Talcum Powder Products.

Over the years, Dr. Crowley has developed many pharmaceutical formulations, nutritional supplements, and food products, including developing over 50 formulations that have been tested in human clinical studies.[138] He has authored or co-authored over 15 clinical study protocols and over 30 published articles and abstracts and four book chapters relating to his work.[139] He is an inventor of five United States patents and a number of foreign patents and pending applications.[140] He has served as a reviewer for many peer-reviewed journals.[141]

Perhaps most relevant to his task in this litigation is Dr. Crowley's experience creating chemical formulas for various pharmaceutical and cosmetic products. Examples include: formulating a fragrance for use in a prenatal vitamin;[142] formulating a cosmetic facial mask;[143] and formulating pharmaceutical products for

[138] Crowley Report at 14; Crowley Dep. at 342:1-11.

[139] Crowley Report at 14-15.

[140] *Id.* at 15.

[141] *Id.* at 15.

[142] Crowley Dep. at 52:14-23.

[143] *Id.* at 52:3-5.

vaginal use, including Crinone and vaginosis and fungal vaginosis products.[144] As part of Dr. Crowley's work in the field of chemical formulation, he regularly reviews the safety profiles of chemicals to determine whether they are safe to use in his customers' products. That is precisely what he did in this litigation.

2. Dr. Crowley employed the same thorough, systematic methodology to review the fragrance chemicals in the J&J Talcum Powder Products that he regularly uses in his own work with consumer products

J&J tries to discredit Dr. Crowley's methodology as merely "plugging the names of the chemicals into Google or PubChem to see what he could find."[145] However, Dr. Crowley described his actual methodology in detail at his deposition and it is the same process that he regularly uses as a chemist and chemical formulator for consumer products—in sum, he reviewed the totality of available safety data for each fragrance chemical used in J&J Talcum Powder Products: "I tried to examine the totality of the evidence for each and every chemical and collate that…in a meaningful way to examine their properties and to answer the questions that were posed to me.[146]

First, Dr. Crowley took the list of fragrance chemicals used in J&J *Baby Powder* and *Shower-to-Shower* and tried to identify a CAS (Chemical Abstracts

[144] *Id.* at 205:1-9.

[145] Def. Mem. at 9. (internal quotations omitted).

[146] Crowley Dep. at 111:7-15.

Service) number for each so he could cross-reference it with various databases and gather physical and chemical properties, as well as safety profiles, in vitro and/or in vivo studies, and any published or known pharmacological properties about the chemicals.[147] He reviewed the IFRA (International Fragrance Association), CIR (Cosmetic Ingredient Review), and FDA (Food and Drug Administration) websites, particularly the FDA's Inactive Ingredient Database.[148] He reviewed journals, including Food and Chemical Toxicology, to see what studies were available, as well as the EFSA (European Food Safety Authority) website, and the RTECS (Registry of Toxic Effects of Chemical Substances) website, all with the goal of gathering as much pertinent information about the chemicals as possible.[149] He classified the chemicals according to whether they are established irritants, sensitizers, or allergens.[150] He then compiled all of his relevant findings into detailed tables and appendices in his report.

Dr. Crowley explained that this is exactly what "a standard formulator "like himself does to determine whether chemicals are safe to use in consumer products.[151] As he put it:

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[147] *Id.* at 109:13-19.

[148] *Id.* at 109:20-23.

[149] *Id.* at 110:1-22.

[150] *Id.* at 110:8-13.

[151] *Id.* at 112:23-113:4.

> Let's be clear about this. When companies engage me to help them build products, they don't want me to take any unnecessary risks… So, ideally, you use excipients and active ingredients that are listed by the FDA, have a CIR monograph or safety study, you know, are listed in the Food Chemical Codex, have a full – published in a peer-reviewed journal safety study. So more often than not, the generally-accepted standard is to go use chemicals that meet all those criteria…there's risk associated with using things that don't.[152]

Accordingly, Dr. Crowley looked to the available regulatory information, studies, and technical literature on these issues and opined as to whether someone in the chemical formulation industry like himself would have concerns about using those chemicals in consumer products, either because of regulatory issues or because of their potential to contribute inflammatory, toxic, and/or potentially carcinogenic properties to the products.[153]

3. Dr. Crowley has ample "good grounds" to support his opinions about the fragrance chemicals in J&J Talcum Powder Products and there is nothing "haphazard" about his methodology

[152] *Id.* at 186:22-187:12.

[153] To the extent J&J criticizes Dr. Crowley for not performing his own "risk analysis" of each chemical, he explained that he did not need to do so because that work has "already been done and published in the literature." Crowley Dep. at 132:20-133:2. *Daubert* requires the proponent of the scientific evidence to show that the expert's conclusion has been arrived at "in a scientifically sound and methodologically reliable fashion," not that the expert's opinion or methodology is beyond reproach. *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998); *In re TMI Litigation*, 193 F.3d 613, 665 (3rd Cir. 1999) (explaining that plaintiffs "do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are correct, they only have to demonstrate by a preponderance of evidence that their opinions are reliable" (citation omitted)).

J&J argues that Dr. Crowley's review of the chemicals was "haphazard" and that his opinions "lack good grounds." However, a closer analysis reveals that J&J itself has a "haphazard" understanding of the chemicals used in its own products and the way those chemicals are classified by regulatory bodies.

- **Styrene (Benzene, ethenyl-)**: At Dr. Crowley's deposition, counsel for J&J incorrectly stated that styrene has an IARC Group 2B classification, meaning that it is "possibly" carcinogenic to humans."[154] Remarkably, J&J *yet again* incorrectly categorizes styrene in its brief, this time claiming that it has an IARC Group 3 classification.[155] Dr. Crowley corrected J&J's first misclassification error at his deposition—styrene is classified by IARC in the 2A group, meaning that it is "*probably* carcinogenic to humans."[156] As Dr. Crowley explained:

  "IARC 2A is probably carcinogenic to humans. It means limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies or inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals, and strong evidence that the carcinogen is meted by a mechanism that does operate in humans."[157]

  Dr. Crowley also testified that the National Toxicology Program has determined that styrene is

[154] Crowley Dep. at 244:13-14.

[155] Def. Mem.at 40.

[156] **Exhibit 11**, IARC 2A classification for styrene.

[157] Crowley Dep. at 358:5-18.

reasonably anticipated to be a human carcinogen.[158] Dr. Crowley provides numerous sources for his conclusions regarding styrene in his report, including, but not limited to: styrene has been implicated as a reproductive toxicant, neurotoxicant, or carcinogen in vivo or in vitro; the *FDA has banned styrene's use as a synthetic flavoring substance; styrene has been observed to cross the placenta in studies;* styrene's metabolite styrene 7,8-oxide is genotoxic; and styrene has been linked to cytogenic, DNA damage, DNA inhibition, sister chromatid exchange, and unscheduled DNA synthesis in multiple in vitro models.[159]

Indeed, the information provided by J&J regarding compositional changes to its Talcum Powder Products indicates that J&J *decided to remove styrene* from the products around 2014.[160] Accordingly, there is more than ample basis for Dr. Crowley to reach his conclusion that the use of styrene in consumer cosmetic products like J&J *Baby Powder* and *Shower-to-Shower* poses both regulatory concerns and can contribute to the inflammatory properties, toxicity, and/or potential carcinogenicity of the Talcum Powder Products as a whole.

- **Coumarin, Eugenol, and D-limonene**: While J&J is correct that coumarin, eugenol, and D-limonene (unlike styrene) have IARC Group 3 classifications, J&J presents an incomplete definition of what that

[158] *Id.* at 359:13-18.

[159] Crowley Report at 22-23 (emphasis supplied); *see also* Crowley Dep. at 255:7-13 ("Styrene 7,8-oxide has been implicated and found to be carcinogenic and genotoxic in virtually every study that has ever been done with it. Metabolism of styrene to those metabolites have also been demonstrated both in humans and in animals to be carcinogenic.").

[160] Crowley Dep. at 142:10-14; Crowley Report at 13, fn. 1.

classification means, and ignores the other data Dr. Crowley relies on to reach his conclusions about the chemicals' ability to contribute to the inflammatory, toxic, and/or carcinogenic properties of the Talcum Powder Products.

It is incomplete to describe IARC Group 3 chemicals as "not classifiable" as to carcinogenicity because there is "inadequate evidence that the substance causes cancer in humans."[161] J&J offered the same half-explanation at Dr. Crowley's deposition, and he supplied the remaining pertinent information at that time. In Dr. Crowley's own words: "No. That's only half of it. The other part of that is evidence of carcinogenicity is inadequate in humans *but sufficient in experimental animals*, but strong evidence that the mechanism of carcinogenicity in experimental animals *may not operate in humans*, or agents that don't fall into any other group."[162] In other words—there is evidence of carcinogenicity in animal studies, but it is *not yet fully established* whether the carcinogenic mechanism operates similarly in humans.

Accordingly, Dr. Crowley is not mistaken in saying that coumarin, eugenol, and d-limonene are "potential carcinogens" because there is "sufficient" evidence of those chemicals' carcinogenicity in animals, while human carcinogenicity is simply not yet established. *Coumarin has been banned in foods since 1954, it is not listed by the CIR, a 2018 study links it to the development of liver tumors in rats and mice* and Clara cell toxicity and lung tumors in mice, it causes fetotoxicity in rats, and it results in sister chromatid exchange in hamster ovary cells.[163]

[161] Def. Mem. at 40-41.

[162] Crowley Dep. at 239:1-8 (emphasis supplied).

[163] Crowley Report at 23-24.

Eugenol has been shown to cause sister chromatid exchange and chromosome aberration in hamster ovary cells.[164] Likewise, *D-limonene causes reproductive effects in mice and rats following oral administration and cytotoxicity in hamster ovary cells.*[165] All of this information taken together is sufficient to support Dr. Crowley's opinion that coumarin, eugenol, and d-limonene can contribute to the inflammatory properties, toxicity, and/or carcinogenicity of J&J *Baby Powder* and *Shower-to-Shower*.

- **Benzophenone:** J&J challenges Dr. Crowley's conclusions about benzophenone, which was recently removed from use in foods by the FDA, because the 2006 NTP study (National Toxicology Program) he cited "did not conclude that benzophenone can cause ovarian cancer."[166] Benzophenone is an IARC Group 2B chemical, meaning it is possibly carcinogenic to humans.[167] It is no longer listed in the CFR for food use and it has no IFRA standard.[168] It is associated with an increased risk of "hepatoblastoma in male mice, histiocytic sarcoma in female mice, increased incidence of mononuclear cell leukemia in male and female rats[,] [r]enal tube adenoma in male rats, histiocytic sarcoma in female rats, and tumors in the kidney."[169] And importantly, the 2006 NTP study that J&J references *does link benzophenone to ovarian abnormalities*. Dr. Crowley read from the NTP report in pertinent part at his deposition:

[164] *Id.* at 24.

[165] *Id.* at 21.

[166] Def. Mem. at 41.

[167] Crowley Dep. at 276:17-21.

[168] Crowley Report at 47.

[169] Crowley Dep. at 277:10-16.

> So this is from the NTP report, and I'm going to read it. Histiocytic sarcoma in females. There was a positive trend in the incidence of histiocytic sarcomas, all organs…In the current two-year study, only females were affected, and the liver and lung were involved in all affected females. The histiocytic sarcomas were highly invasive in all three 1,250 PPM mice. *Multiple organs throughout the body had neoplastic histiocytic legions; ovaries*, *uterus*, spleen, adrenal gland, kidney, urinary bladder, and multiple lymph nodes were affected in all three animals."[170]

> As Dr. Crowley stated, "frankly, [the] NTP is extraordinarily thorough."[171] The NTP study showed that male rats receiving benzophenone had severe kidney nephropathy, kidney tumors, and leukemia.[172] Female rats had higher rates of leukemia, liver tumors, increased severities of kidney nephrology, metaplasia, epithelia of the nose and hyperplasia of the spleen.[173] The NTP program also concluded that benzophenone caused cancer – kidney cancer in male rats, liver tumors in male mice, and histiocytic sarcomas in female mice."[174] Additionally, "in vivo estrogenic activity of benzophenone was confirmed in the uterotrophic assay" by IARC in 2013.[175] This abundance of data more than supports Dr. Crowley's opinions regarding benzophenone and its ability to contribute

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[170] *Id.* at 279:12-280:13 (emphasis supplied).

[171] *Id.* at 277:23-24.

[172] *Id.* at 278:1-4.

[173] *Id.* at 278:4-8.

[174] *Id.* at 277:21-278:16.

[175] Crowley Report at 48.

to the inflammatory properties, toxicity, and/or carcinogenicity of J&J Talcum Powder Products.

- **P-cresol:** J&J's challenge to Dr. Crowley's opinions regarding p-cresol rests on a single review from the Agency for Toxic Substances and Disease Registry, which concluded that there is inadequate information to assess p-cresol's carcinogenic potential.[176] However, the EPA has categorized p-cresol as "possibly carcinogenic" from 1990 to the present day.[177] Studies show that p-cresol is cytogenetic in hamster ovary cells and causes DNA damage in human lymphocytes.[178] In 2006, the CIR (Cosmetic Ingredient Review Expert Panel) found that "in the p-cresol assay…there were significant increases in chromosomal aberrations at all concentrations tested," and "p-cresol was considered positive for inducing chromosomal aberrations in CHO cells under both activation and nonactivation conditions."[179] Further, the **CIR does not permit p-cresol for use in cosmetics that are applied to mucous membranes**.[180] Older studies demonstrated that women exposed in the workplace to varnishes containing mixed cresols had increased gynecological problems such as menstrual disorders and hormonal disturbances, and an increased frequency of perinatal mortality and abnormal

[176] Def. Mem. at 42.

[177] *See* https://www.epa.gov/sites/production/files/2016-09/documents/cresol-cresylic-acid.pdf (last accessed May 22, 2019); p. 1, Hazard Summary: "Several animal studies suggest that o-cresol, m-cresol, and p-cresol may act as tumor promotors. EPA has classified o-cresol, m-cresol, and p-cresol as Group C, possible human carcinogens."

[178] Crowley Report at 25, citing RTECS.

[179] *Id.* at 25.

[180] *Id.* at 25, citing Cosmetic Ingredient Review Expert Panel, 2006 (emphasis supplied).

development of newborn infants.[181] Here again, there is sufficient data to support Dr. Crowley's opinion regarding p-cresol's contribution to the inflammatory properties, toxicity, and/or carcinogenicity of J&J Talcum Powder Products, and a single review from the Agency for Toxic Substances and Disease Registry does not discredit all other evidence.

- **Musk ketone:** J&J discusses musk ketone in its brief, but doesn't explain what, if anything, was inaccurate or "haphazard" about Dr. Crowley's review of the chemical. J&J is correct—musk ketone is classified as a Category 3 carcinogen by SCHER (Scientific Committee on Health and Environmental Risks), and is suspected of being a carcinogen.[182] It is also identified as "a strong inducer of phase I enzymes in rodents and co-genotoxicant in vitro in human derived cells in rather low doses, suggesting that exposure to musk ketone might increase the susceptibility to health hazards caused by carcinogens in humans."[183]

- **Myroxylon Pereirae (Balsam peru) Oil**: J&J dramatizes a simple misunderstanding regarding the distinction between balsam peru *crude* and balsam peru *extract/distillate*—a misunderstanding prompted by J&J's use of the phrase "balsam peru oil" in its documents. Dr. Crowley easily explained the issue at his deposition—both balsam peru crude and balsam peru extract/distillate have the same CAS (Chemical Abstracts Service) number.[184] Dr. Crowley used CAS numbers as part of his process of

[181] *Id.* at 26, citing Syrowadko & Malysheva, 1977.

[182] *Id.* at 51.

[183] *Id.* at 51, citing Schmeiser, Gminski, & Mersch-Sundermann, 2001.

[184] Crowley Dep. at 171:23-172:3.

> identifying and researching the chemicals. However, Dr. Crowley had no way of knowing with absolute certainty whether J&J's use of the phrase "balsam peru oil" refers to the crude or extract/distillate version: **Q**. "And what you know is that Peru balsam crude is not the ingredient that is in the *Baby Powder* or *Shower-to-Shower* powder. Correct? **A**. I don't know that."[185] Dr. Crowley ultimately testified that he takes J&J at its word that the "restricted" balsam peru extract/distillate is used in J&J *Baby Powder* rather than the "prohibited" balsam peru crude.[186] However, this issue does not affect or change Dr. Crowley's overall opinions about the fragrance chemicals used in the J&J Talcum Powder Products.[187]

There is an abundance of information and data supporting Dr. Crowley's opinions about the fragrance chemicals used in J&J Talcum Powder Products. The evidence is laid out in detail in his report—particularly in Appendices A and B—and was explained in even greater detail at his deposition. J&J's strained attempt to characterize Dr. Crowley's review as "haphazard" rests solely on J&J's own misunderstanding of certain chemical classifications (i.e. styrene), disregard for data

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[185] *Id.* at 170:18-23.

[186] *Id.* at 172:5-173:3.

[187] Further, any mistakes in Dr. Crowley's report should be addressed in cross examination, not result in the wholesale exclusion of his opinions. "Indeed, federal courts have generally found that 'the perceived flaws' in an expert's testimony often should be treated as 'matters properly to be tested in the crucible of the adversarial system, 'not as 'the basis for truncating that process.'" *Violas v. GMC*, 73 F.Supp 2d 452, 462 (D.N.J. 1999). (*quoting Walker v. Yellow Freigh Sys.,Inc.* Civ. A. No. 98-3565, 1999 WL 757022, at *8 (E.D. La. Sep. 24, 1999)).

that doesn't support J&J's position, and nit-picking at minor discrepancies. J&J has not established that Dr. Crowley "lacks good grounds" for his opinions, and they should not be excluded on that basis.[188]

4. There is ample scientific evidence linking the fragrance chemicals used in J&J Talcum Powder Products to cancer, including ovarian cancer

J&J attempts to diminish Dr. Crowley's substantial and compelling evidence that the fragrance chemicals are problematic from a regulatory standpoint and can contribute to the inflammatory, toxic, and carcinogenic properties of the Talcum Powder Products, by emphasizing that there are no *human* studies examining the chemicals' impact on *human ovaries*.[189] But of course, it is not ethically possible to test for the carcinogenicity and toxicity of chemicals on human ovaries—studies can *only* be performed on animals. Dr. Crowley explained this repeatedly at his deposition:

- "And you don't do those kind of studies against humans. They're unethical. Right? So the safety of d-limonene has not been established in human vaginas."[190]
- "Just so we're clear, it's unethical to infuse human ovaries with para-cresol or any of these. That's just not done."[191]

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[189] Def. Mem. at 44.

[190] Crowley Dep. at 222:4-7.

[191] *Id.* at 282:9-12.

- "I don't think that any regulatory authority in the world would allow me to administer para-cresol to a human ovary. It wouldn't happen."[192]
- Regarding p-cresol studies in humans: "So to make that assertation in humans is not ethically possible. Those studies are done in animals."[193]

- Regarding p-cresol studies: "All three of those studies are done with cell lines. They are in vitro, because we don't ethically endanger humans…"[194]

- Regarding styrene studies in humans: "Yeah, so as we've talked about, those studies are unethical, and that's why there aren't any."[195]

These ethical considerations require us to rely in large part on animal studies for assessing the possible toxicity and/or carcinogenicity of chemicals—and the animal studies linking the specific fragrance chemicals in J&J Talcum Powder Products to cancer (including the ovaries) are numerous. Dr. Crowley identifies the studies in his report, and he also listed the fragrance chemicals in *Baby Powder* that have specifically been linked to *ovarian* abnormalities in animal studies at his deposition:

[192] *Id.* at 283:17-20.

[193] *Id.* at 283:23-284:1.

[194] *Id.* at 285:21-23.

[195] *Id.* at 364:13-15.

- "So benzaldehyde, sister chromatid exchange, which is a mutation, in Chinese hamster *ovary cells*. That was published by Galloway in '87."[196]

- "Ethyl methylphenylglycidate sister chromatid exchange and chromosomal aberrations in Chinese hamster *ovary cells*, Galloway, 1987. European Food Safety Authority, same substance. There's substantial evidence of a genotoxic potential from the available in vitro and in vivo studies."[197]

- "Eugenol, sister chromatid exchange and chromosomal aberrations in Chinese hamster *ovary cells*, Galloway, 1987."[198]

- "Styrax oil, sister chromatid exchange in Chinese hamster *ovary cells*, Gulati, Witt, Anderson, Zeiger & Shelby, 1989."[199]

- "para-Cresol, cytogenetic in Chinese hamster *ovary cells*, DNA damage in human lymphocytes, morphologic transformations in mice, RTECS, the Cosmetic Ingredient Review Panel, 2006."[200]

- "para-Cymene, cytotoxic against Chinese hamster *ovary cells*."[201]

- "Propanedioic acid, diethyl ester, tumorigenic in mice following oral dosing, RTECS."[202]

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[196] *Id.* at 115:14-17 (emphasis supplied); *see also* Crowley Report at 22.

[197] Crowley Dep. at 118:3-10 (emphasis supplied).

[198] *Id.* at 118:11-13 (emphasis supplied).

[199] *Id.* at 118:14-17 (emphasis supplied).

[200] *Id.* at 118:18-22 (emphasis supplied).

[201] *Id.* at 119:3-4 (emphasis supplied).

[202] *Id.* at 119:6-8.

And while it is not ethically possible to expose human beings and/or human ovaries to potentially toxic and/or carcinogenic chemicals, studies do exist demonstrating a link between some of the fragrance chemicals in the J&J Talcum Powder Products and toxicity and/or carcinogenicity in humans. For example, counsel for J&J asked Dr. Crowley at his deposition if he was aware of any such study in humans with respect to p-cresol or para-cresol. Dr. Crowley cited a 2006 study from The International Journal of Toxicology: "The safety of Cresols was reviewed by the World Health Organization in 1995. The WHO report concluded there is clear evidence in humans that during dermal or oral exposure, high concentrations of Cresols are corrosive, absorb rapidly, and produce severe toxicity that may result in death."[203] Other examples of studies looking at human exposure include:

- Lavandula Angustifolia (Lavender) Oil: This study has demonstrated that lavender oil is cytotoxic to *human skin cells in vitro* (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR) (Prashar, Locke, & Evans, 2004).[204]

- P-cresol: "Cytogenetic in Chinese Hamster Ovary cells, DNA Damage in *human lymphocytes*, and morphologic transformation in mouse fibroblast (RTECS)."[205]

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[203] *Id.* at 284:13-23; **Exhibit 60** (2006 p-cresol study).

[204] Crowley Report at 24 (emphasis supplied).

[205] *Id.* at 25 (emphasis supplied).

- P-cresol: "*Women exposed in their workplace* (enamel-insulated wire manufacturing) to varnishes that contained Mixed Cresols (amount not stated) had *increased gynecological problems* such as menstrual disorders and hormonal disturbances. An increased frequency of *perinatal mortality and abnormal development of newborn infants* was also reported Syrowadko and Malysheva (1977) (Syrowadko & Malysheva, 1977)."[206]

Dr. Crowley states in his report that while animal studies are not completely definitive as to whether the same effects will be observed in humans, they are indicators of biological activity.[207] He testified that IARC considers both human (when available) and animal studies when classifying chemicals. [208]But, the "absence of human studies" does not mean "that somehow these [chemicals] are safe. That's not the conclusion that a person of skill in the art would conclude."[209] In other words, someone in the business of assessing chemicals for use in consumer products like Dr. Crowley would not determine that a chemical is safe for human use simply because *no human studies exist* saying otherwise—and particularly not when *numerous* animal studies exist demonstrating that the chemical has toxic and/or carcinogenic properties and when those studies are "indicators of biological activity." Dr. Crowley explained that the established biological activity or biological

[206] *Id.* at 26 (emphasis supplied).

[207] *Id.* at 48.

[208] Crowley Dep. at 261:14-17.

[209] *Id.* at 274:2-8.

mechanism for both the initiation and progression of cancer here is *inflammation*. "I have found studies that link inflammation to cancer. That's an established link. That's indisputable. The Canadians stated as much in their assessment on perineal application of talc, and these fragrance chemicals are part of that product."[210]

The abundance of evidence provided by animal studies support Dr. Crowley's conclusion that the fragrance chemicals raise regulatory concerns and can contribute to the inflammatory properties, toxicity, and/or potential carcinogenicity of J&J's Talcum Powder Products as a whole.

5. It was not necessary for Dr. Crowley to consider dose response to form his opinions about the fragrance chemicals in J&J Talcum Powder Products

J&J argues Dr. Crowley's opinions are flawed because he did not conduct a "dose-response assessment."[211] This argument fails for several reasons. *First*, Dr. Crowley testified that even assuming *arguendo* it was necessary to do a dose-response assessment, he couldn't because J&J did not supply the necessary information for such an analysis.[212] J&J now suggests that it would have been appropriate for Dr. Crowley to "roughly estimate" the amount of each individual

[210] *Id.* at 308:2-7.

[211] Def. Mem. at 51.

[212] *See, e.g.*, Crowley Dep. at 201:3-5; 302:14- 18; 309:18-20.

chemical in *Baby Powder* and *Shower-to-Shower* and use "relative portions" to perform dose assessments.

J&J provided limited, incomplete information about the fragrance chemicals in its products. For example, J&J's fragrance composition documents do not specify the precise amount of each individual chemical in the products, but only "relative portions." J&J also does not explain whether the "relative portions" of each chemical remained uniform over the many decades that the products have been on the market. It is absurd for J&J to suggest that Dr. Crowley was required to conduct a dose assessment after failing to provide him with *all of the information* he would need to do so in a scientifically sound and accurate manner. Dr. Crowley explained why it is not appropriate to hazard a guess about dosage and exposure, particularly when J&J did not provide him with the information necessary to undertake such an analysis:

> So, for example, cinnamal has a Category 5 restriction of 0.05 percent. Since I don't know how much is present, I can't make a judgment as to whether the cinnamal present in *Baby Powder* exceeds 0.05 percent or not. There's a bunch of other fragrance chemicals here too that have these restrictions similar to *Shower-to-Shower*. Let's save each other some time. I can't make that judgment because your client hasn't given me the information to be able to do that."[213]

[213] *Id.* at 330:15-331:2.

Regardless, Dr. Crowley did not need to conduct a dose-response assessment on the fragrance chemicals for the same reasons discussed above regarding heavy metals. Dr. Crowley is not offering a causation opinion regarding whether exposure to the individual chemicals causes ovarian cancer. He is opining as to whether those chemicals—based on all available data and studies—can contribute to the inflammatory properties, toxicity, and/or carcinogenicity *of the J&J Talcum Powder Products as a whole*. Again, the proper methodology for mixtures is a non-threshold model with consideration given to the additive effects of the components. A qualitative analysis is appropriate for mixtures, particularly where there is inadequate quantitative data available (or provided by J&J) and exposures cannot be characterized with confidence. And like the heavy metals discussed above, the many studies and data compiled by Dr. Crowley about the fragrance chemicals in the J&J Talcum Powder Products establish a biologically plausible mode of action/mechanism for the promotion of carcinogenesis:

> I mean, I've stated fairly clearly, I feel, that…you've got a whole bunch of irritants, you've got a whole bunch of sensitizers, and you've got a whole bunch of allergens that have been glued to talc particles, administered to the peritoneal area, which subsequently enters the vagina, and where that talc particle goes, those fragrance chemicals go with it. They have demonstrated—many of them—*demonstrated biological activity in animal and in vitro cell models that demonstrates toxicity and carcinogenicity*. And so…I don't know how else to state it. I think *they can*

> *absolutely contribute to the carcinogenicity of the product in total*.[214]

Dr. Crowley repeatedly explained that inflammation is a well-established biologic mechanism for both the initiation and progression of cancer, including ovarian cancer:

- "But also…those inflammatory chemicals travel throughout the human body. So increased levels of inflammation have been associated with a higher risk of cancers."[215]
- "I have found studies that link inflammation to cancer. That's an established link. That's indisputable. The Canadians stated as much in their assessment on perineal application of talc, and these fragrance chemicals are part of that product."[216]
- "I can also point you to the Canadian assessment on the safety of talc where they also stated that chronic inflammation and oxidative stress are important factors in the development and behavior of cancer, *including ovarian cancer*."[217]

Dr. Crowley further explained that performing a dose assessment of the individual fragrance chemicals in a mixture would be problematic because it wouldn't take into consideration additive effects—that is, chemicals in combination

[214] *Id.* at 327:20-328:13 (emphasis supplied).

[215] *Id.* at 82:18-22.

[216] *Id.* at 308:2-7.

[217] *Id.* at 310:5-11 (emphasis supplied).

with one another can and do behave differently than they behave individually: "Another consideration is…the safety studies are usually single ingredient safety studies…if we were to do a safety study of para-Cresol in an animal, it would be simply that. It wouldn't be para-Cresol and another 142 other chemicals. Right? So very likely there's additive effects.."[218] Dr. Plunkett similarly explained: "when you have a complex mixture that has added to it things like asbestos and heavy metals, because I talk about the *additivity issue that can come to play*…in other words, [there is an] increased risk when you have a complex mixture with additional components that all share the same toxic properties as far as target organs or types of effects or mechanisms that are triggered in the body."[219]

For example, at least one of the fragrance chemicals in the J&J Talcum Powder Products—p-cresol—is "co-carcinogenic," which means it has been found to "promote tumors in animals when co-administered with a known carcinogen."[220] This is an extremely important point when it comes to assessing mixtures—even a chemical that may not itself be classified as a known carcinogen *can increase a carcinogen's activity* when they are administered together.[221] Assessing dose

[218] *Id.* at 355:19-356:2.

[219] Plunkett Dep. at 146:11-21 (emphasis supplied).

[220] Crowley Dep. at 212:9-13; Crowley Report at 21.

[221] *Id.* at 361:9-13.

response for each individual component of mixtures like fragrances (or the J&J Talcum Powder Products themselves) would not provide a complete or accurate account of the mixture's *total* inflammatory, toxic, and/or carcinogenic effects.

Finally, Dr. Crowley explained that dose response is immaterial with respect to genotoxic materials—"genotoxic materials do not live under a dose response relationship. If it's been classified as genotoxic, one molecule is enough to cause an increase in risk associated with that particular compound."[222] Dr. Crowley identified several genotoxic and potentially genotoxic fragrance chemicals in his report, including: linalyl acetate;[223] citral;[224] diethyl phthalate;[225] Ethyl Methylphenylglycidate;[226] and benzaldehyde.[227] Additionally, at least one of the fragrance chemicals—styrene—has a known genotoxic metabolite: "Styrene-7,8-oxide has been implicated and found to be carcinogenic and genotoxic in virtually

[222] *Id.* at 131:22-132:3.

[223] Crowley Report at 25 ("The genotoxicity of linalyl acetate described here in mammalian cells strengthens the data obtained in the bacterial ones and highlights the need of in vivo studies.").

[224] *Id.* at 23 ("Valid genotoxicity (induction of sister chromatid exchange) result in Chinese hamster ovary cells…).

[225] *Id.* at 48 ("Diethyl Phthalate, a non-fragrance present as a component in the fragrance mixture, is a phthalate ester which are reported to be endocrine disruptors, cause reproductive and developmental toxicities, and potentially genotoxic.").

[226] *Id.* at 24 ("There is substantial evidence of a genotoxic potential from the available in vitro and in vivo studies.").

[227] *Id.* at 22 ("May have a significant genotoxic effect").

every study that has ever been done with it. Metabolism of styrene to those metabolites have also been demonstrated both in humans and in animals to be carcinogenic."[228] A threshold approach based on dose response is not appropriate for genotoxic materials because "They don't have a threshold. One molecule is enough to cause an increased risk."[229]

For all of the foregoing reasons, Dr. Crowley's opinions should not be excluded simply because he did not perform a dose response assessment.

6. The opinions of the PSC's other experts who cite Dr. Crowley's opinions should be not excluded

For all of the reasons set forth above, Dr. Crowley's opinions are reliable and have more than sufficient "good grounds" because his methodology was appropriate. Moreover, his opinions are supported by ample scientific data, regulatory information, and Dr. Crowley's own extensive experience as a chemist and chemical formulator. Accordingly, there is no basis for excluding any other of the PSC's experts' opinions that relate to or rely on Dr. Crowley's opinions.

[228] Crowley Dep. at 255:7-13.

[229] *Id.* at 125:20-126:1.

C. THE PSC's EXPERTS' OPINIONS REGARDING FIBROUS TALC DO NOT REST ON AN "ERRONEOUS" DEFINITION

J&J argues that the PSC's experts incorrectly interpret the definition of "fibrous talc," and use a definition that differs from the IARC definition.[230] This is misleading at best—IARC has classified fibrous talc as a Group I carcinogen. In fact, IARC devoted multiple Monograph reviews to fibrous (asbestiform) talc in order to *clarify* any confusion regarding the definition.

Amphiboles may undergo incomplete alteration to form transition fibers, composed of both fibrous talc and amphibole, or they may be replaced with fibrous talc and serpentine.[231] In 1987, IARC evaluated the carcinogenicity of talc and concluded that there was sufficient evidence that talc containing asbestiform fibers was carcinogenic to humans.[232] To clarify the terminology, in 2010 IARC stated that "[t]he term '*asbestiform fibre*' has been mistaken as a synonym for 'asbestos fibre' when it should be understood to mean *any mineral, including talc*, when it grows in

[230] Def. Mem. at 57.

[231] Van Gosen, B.S., Lowers, H.A., Sutley, S.J., et al. "Using the geologic setting of talc deposits as an indicator of amphibole asbestos content," Env Geol (2004) 45:920. https://doi.org/10.1007/s00254-003-0955-2. **Exhibit 65**

[232] IARC Monograph on Silica and Some Silicates (1987), relevant excerpts attached hereto as **Exhibit 61**; IARC Overall Evaluaitons of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, Supplement (1987), relevant excerpts attached hereto as **Exhibit 62**.

an asbestiform habit." [233] At the same time, IARC also re-addressed the issue of carcinogenicity: "The present Working Group also decided to expand the name of the Group-1 agent from 'talc containing asbestiform fibres' to 'talc containing asbestos *or other asbestiform fibres*.'" [234] This allowed for the inclusion of "other asbestiform fibers"—like talc in asbestiform habit.

IARC, 2012 states that "the conclusions reached…about asbestos and its carcinogenic risks apply to these six types of fibres [chrysotile, actinolite, amosite, anthophyllite, crocidolite, and tremolite] wherever they are found, and *that includes talc containing asbestiform fibres*." [235] IARC, 2012 further differentiates the types of talc, stating that "[t]alc may also form true mineral fibres that are asbestiform in habit."[236]

Throughout the evolution of the definition of fibrous talc, two IARC definitions are the most important: 1) the term "*asbestiform fiber*," which is defined by IARC as any mineral, *including talc, when it grows in an asbestiform habit;*[237] and 2) IARC's assertion that asbestos and its risks apply to chrysotile, actinolite,

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[233] IARC Monograph on Carbon Black, Titanium Dioxide, and Talc, Volume 93 (2010) at 39 (emphasis supplied), relevant excerpts attached hereto as **Exhibit 63**.

[234] IARC, 2010 (**Exhibit 63**) at 39 (emphasis supplied).

[235] IARC, 2012 at 219 (emphasis supplied).

[236] IARC, 2012 at 230.

[237] IARC, 2010 (**Exhibit 63**) at 39 (emphasis supplied).

amosite, anthophyllite, crocidolite, and tremolite (types of asbestos), "*and that includes talc containing asbestiform fibres*,"[238] wherein the 'asbestiform fibers' can be either asbestos or asbestiform (fibrous) talc. The PSC's experts all[239] use consistent definitions for 'fibrous talc,' including Drs. Longo and Rigler (i.e., "talc with asbestiform fibers or asbestiform talc.").[240]

Given the clarity of the literature, J&J's arguments 1) that the PSC's experts improperly rely on literature to support opinions that fibrous talc can cause cancer, and 2) that this literature refers to "talc that is intergrown with asbestos,"[241] or "talc intergrown on a nanoscale with other minerals…"[242] (indicating it is talc containing asbestos, rather than talc in asbestiform habit as defined by IARC) are disingenuous and incorrect. [243] Based on the IARC, 2012 definitions, the carcinogenic risks that apply to asbestos (a Group I carcinogen) also apply to fibrous talc. As a result, the

[238] IARC, 2012 at 219 (emphasis supplied).

[239] The PSC's experts being criticized by J&J includes Drs. Longo, Rigler, McTiernan, Smith, Wolf, Plunkett, Zelikoff, Cook, Singh and Smith-Bindman.

[240] Longo's definition of 'fibrous talc' as reiterated in J&J's "Heavy Metals and Fragrances" brief at 58.

[241] Def. Mem. at 3, 57.

[242] Def. Mem. at 60.

[243] J&J criticizes the PSC's experts Drs. McTiernan, Smith, Wolf, Plunkett, Zelikoff, Cook, Singh, Smith-Bindman and Krekeler (Def. Mem. at 58-59, and 61.).

PSC's experts Longo and Rigler included asbestos fibers *as well as fibrous talc* in their analyses of the J&J talcum powder product samples.[244]

J&J argues that IARC "clearly states" that elongated mineral fragments "not 'intergrown' with asbestos – i.e., the talc that Drs. Longo and Rigler call fibrous talc – are not carcinogenic."[245] In support, J&J quotes a passage from IARC, stating it is applicable to talc. In reality, the quote omits a portion of the passage that makes it clear the reference is to other mineral fragments that can occur in asbestiform habit to constitute asbestos—the reference is improperly quoted and inapplicable.

J&J quotes the following passage to apply to talc:

> …talc **"may…be elongated without being asbestiform"** and therefore without being dangerous.[246] (underline added).

The full quote reads:

> Asbestos is a commercial term that describes six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite (IARC, 1977). Similarly, to talc, these six minerals occur more commonly in a non-asbestiform habit, and **may also be elongated without being asbestiform.** Actinolite, anthophyllite and tremolite may occur in some talc deposits; when asbestiform, they constitute asbestos…[247]

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[244] Longo MDL Report at 1-6.

[245] Def. Mem. at 60.

[246] Def. Mem. at 61, citing to IARC, 2010 at 277.

[247] IARC, 2010 (**Exhibit 63**) at 277.

The passage quoted by J&J *actually* clearly indicates that the six listed minerals (actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite) may be elongated without being asbestiform—not talc, as J&J alleges. The phrase "may also be elongated" in the passage refers to the minerals potentially being asbestos, as indicated in the previous sentence, or elongated, as in the cited sentence. J&J has improperly quoted IARC, 2010 to generate an incorrect standard.[248]

J&J also argues that Drs. Cook and Krekeler cite to internal documents as evidence of the presence of fibers or fibrous talc without any basis for assuming the fibers referenced were asbestos or asbestiform.[249] Here again, this argument attempts to conflate the terms "asbestos" and "asbestiform"—a misconception that IARC has endeavored to clarify since "asbestiform fibers" were classified as carcinogenic in 1987. J&J makes the bold assertion that talc is "only rarely fibrous"—and cites IARC, 2012 for support.[250] The 2012 IARC monograph says no such thing, only that while talc particles are "normally plate-like," they "may also form true mineral fibres

[248] Additionally, even when different interpretations can be given to data you have a "classic battle of the experts, a battle in which the jury must decide the victor." *Lanzilotti v. Merrell Dow Pharms.*, Civ. A. No. 82-0183, 1986 WL 7832, at *3 (E.D. Pa. Jul. 10, 1986) (*quoting Ferebee v. Chevon Chemical Co.*, 736 F.2d 1529, 1535 (D.C. Cir. 1984)).

[249] Def. Mem. at 61.

[250] J&J "*Motion to Exclude Plaintiffs' Experts' General Causation Opinions*" at 90.

that are asbestiform in habit"—that is, fibrous talc.[251] Indeed, J&J's own analyses show that fibrous talc occurred in up to **10% of the talc ore** from the Hammondsville Mine in Vermont.[252]

Both IARC, 2012 and IARC, 2010 were dedicated to expounding on definitions *for the inclusion of fibrous talc (talc in asbestiform habit) as a carcinogen*. As discussed above, IARC, 2010 defines the term 'asbestiform fiber' to include talc when grown in asbestiform habit.[253] IARC, 2012 also clearly states that "[t]alc may also form true mineral fibres that are asbestiform in habit."[254] This asbestiform talc is commonly referred to as "fibrous talc." IARC, 2012 states that the carcinogenic risks of asbestos also apply to talc containing asbestos fibers (i.e., asbestiform talc, commonly referred to as fibrous talc).[255]

The examples of fibrous talc cited in Dr. Cook's report were specifically designated as such and came from J&J's own internal reports—many were third-party testing results. J&J also argues that Dr. Cook "admits that many of them did not grow in a fibrous habit at all," but that their shape could be an effect of the

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[251] IARC, 2012 at 230.

[252] **Exhibit 64**, JNJS7IR_000001978-2124, Colorado School of Mines testing at Hammondsville mine in Vermont.

[253] IARC, 2010 (**Exhibit 63**) at 39.

[254] *Id.* at 230.

[255] IARC, 2012 at 210.

milling process. The PSC's experts agree—and their reports clearly state—that both certain amphiboles and talc can grow in both the fibrous and non-fibrous state.[256] They also agree that particle shape can be affected during the milling process.[257] Nonetheless, both fibrous and non-fibrous mineral forms exist, and to assume that minerals specifically labeled as "fibrous" (presumably by experts in the field) are something *other than fibrous* is illogical and unsupported by the evidence. **J&J's argument that the mineral forms identified as fibrous *are not fibrous* contradicts the documents and has no basis in fact.** Accordingly, J&J's attempt to exclude the PSC's experts' opinions regarding the fibrous talc present in *Baby Powder* and *Shower-to-Shower* should be denied.

III. CONCLUSION

J&J's *Motion To Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals and Fragrances In Johnson's Baby Powder and Shower-to-Shower* should be denied. The PSC's experts' opinions regarding the heavy metals, fragrance chemicals, and fibrous talc present in Johnson's *Baby Powder* and *Shower-to-Shower* are well-founded and reliable, and the opinions should not be excluded.

[256] Cook Report at 10, 21; Krekeler Report at 4, 5, 9.

[257] Cook Report at 28.

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